

Case-Fatality and disability of patients with stroke in Iran

Abstract

Background: Few studies have been conducted to assess case-fatality and disability of Iranian patients with stroke. This study was designed to collect morbidity and case-fatality data of hospitalized patients with stroke, in Isfahan, a large city in the central part of Iran.

Methods: From 2006 to 2011, by utilization of overlapping sources (discharge diagnoses, attending physicians, and hospitalization wards), all hospitalized patients with possible strokes were enrolled in the study, and their hospital records were summarized by experienced personnel and reviewed by a neurologist with experience in stroke. Patients with stroke were followed by phone calls or visited their residential addresses and their 28th day functional status was checked by translated version of Modified Rankin Scale. Forms and methods were derived from the World Health Organization MONICA and STEPS projects.

Results: 9487 patients with stroke were identified, mean age 68.98 ± 13.63 years, and 48.3% were females. The in-hospital case-fatality rate was at 16.5% and 28th-day case-fatality rate was at 25.6%. The greatest case-fatality was among patients with intracerebral hemorrhage, and the least case-fatality was among patients with ischemic stroke. Case-fatality was greater among female and older patients, and those with a previous history of stroke. Among survivors, only 26.9% were functionally independent (Modified Rankin Scale <3) which was greatest among patients with subarachnoid hemorrhage and least among patients with intracerebral hemorrhage. None of the patients were admitted to specific stroke units, nor did they receive thrombolytic therapy.

Conclusion: Hospitalized patients with stroke in Isfahan have an unfavorable outcome compared to patients with stroke from developed countries. Low-quality of stroke care may be responsible and urgent attention is needed.

Keywords: Stroke, Case-fatality, Disability evaluation, Epidemiology, Risk factors

Introduction

Stroke has this potential to be the most common cause of death by overtaking heart diseases, although it was the second most common cause of death worldwide at the beginning of 21st century in many reports, and caused approximately 10% of the total deaths.^{1,2} Regional difference in stroke incidence has been emphasized, including the existence of a stroke belt in some countries, but the causes of these disparities have not yet been fully understood.³

One of the most sophisticated measures to reduce stroke case-fatality and morbidity is the utilization of stroke units. It is an area inside of a hospital where physicians, nurses, and other assisting personnel who have high-quality training and experience in stroke management, provide standard care for patients with acute stroke. It has been shown by several studies that management of patients with acute stroke in this type of medical facility reduces death and disability rates by approximately 20% and improves patients' chance of recovery and having independent life.⁴ Intravenous administration of tissue plasminogen activator (t-PA) is the only FDA-approved therapy to re-establish cerebral blood flow during the hyperacute phase of ischemic stroke. Randomized controlled trials actually demonstrate an enormous benefit in patients treated with t-PA compared to control. However, because of increased bleeding risk after 3-4.5 hr. from the beginning of a stroke, few patients (less than 2%) usually benefit from t-PA.⁵ The main reason is that patients who are eligible for treatment don't arrive at the hospital early enough to receive this treatment. In fact, this finding reflects a limited time window as one of the

main obstacles in t-PA administration. Unfortunately, there are few established stroke units at the present time in Iran.

Studies on stroke epidemiology in Iran are scarce. No published study has reported disability outcome of Iranian patients with stroke. Few investigators have reported case-fatality rates among Iranian hospitalized patients with stroke, which were among the greatest ones.^{6,7} In two other cross-sectional, hospital-based studies conducted during 2001 and 2006-2008 in Qom, a well-known religious city of Iran, the case-fatality rate within the first month was reported at 24.6% during 2001, and at 15.3% from 2006 to 2008. Although, these figures showed an apparently declining rate over time in this region, but were still greater than reported ones from western countries and lesser than other developing countries.⁸⁻¹²

This study was designed to collect morbidity and case-fatality data of hospitalized patients with stroke, and the frequency of t-PA use and hospitalization in specific stroke units in all hospitals that admit such patients in Isfahan, a metropolitan city in the center of Iran.

Methods

Population

Isfahan is the third largest city of Iran. Its population is about 2,000,000 inhabitants, and less than 15% of them live in rural areas. Like other parts of the country, it has a young population, with about 55% younger than 30 years, and about 8% older than 55 years.

Hospitals

From 2006 to 2011, six hospitals were mainly admitting patients with stroke in Isfahan, and none of them had the stroke unit. Three of them had specific neurology wards, and all had General Intensive Care Units. In those without neurology wards, patients with stroke were mostly hospitalized in internal medicine wards.

Definition of stroke and diagnostic categories

According to the WHO definition, stroke is a clinical syndrome characterized by rapidly developing neurological symptoms and/or signs, focal and sometimes global (applied to patients in deep coma and those with subarachnoid hemorrhage), with symptoms lasting more than 24 hours unless interrupted by surgery or leading to death, and with no apparent cause other than that of vascular origin.¹³ This definition includes stroke due to cerebral infarction (IS), intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), and subarachnoid hemorrhage (SAH); it excludes subdural hemorrhage, epidural hemorrhage, ICH and brain infarction caused by infection or tumor. With this clinical definition, silent stroke on imaging is not considered a stroke, and imaging confirmation is not required for stroke diagnosis. Hence, the study is based on clinical diagnoses, which has been shown to be reliable.¹⁴ The World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA) project is related to events, not persons.^{7,14} Events are classified as first or recurrent and as fatal or nonfatal. A period of 28 days was used to define the case-fatality rate and to distinguish between events. Diagnostic criteria were applied to symptoms, clinical findings and investigations undertaken within 28 days of onset. Transient ischemic attacks and events associated with trauma, blood diseases or malignancy were excluded.¹⁴ Events were categorized as 'definite stroke', 'not stroke' or 'unclassified'. When the available information permitted a clinical diagnosis, only definite stroke events which fulfilled the criteria were included in this study.

Case finding

Procedures are different according to on how events are identified and registered; either based on admission to hospital ("hot pursuit") or by utilization of post-discharge records to obtain information retrospectively ("cold pursuit").^{15,16} A cold pursuit method was used in this study; records of patients who were hospitalized in either neurology, or other departments under the complete or partial supervision of neurologists in Isfahan hospitals were evaluated for possible signs and symptoms of stroke events. Search for potential stroke records was done by overlapping methods; looking through discharge diagnoses (Stroke, Cerebrovascular Accident, ICH, SAH, Vertebrobasilar Insufficiency, Cerebral Venous Thrombosis, and Transient Ischemic Attack), or records by name of attending and hospital wards. Stroke subtypes were classified by the results of Computed Tomography (CT scan) done on patients presenting with stroke symptoms. Apart from the main six hospitals, patients who possibly had a stroke during hospitalization which were discovered by surveillance department personnel (myocardial infarction surveillance unit) were also included in the registry. All potential stroke records were evaluated by experienced health personnel who was continuously under education in this regard. She summarized proper records in special checklists which were evaluated by a stroke fellow to verify if the stroke was the diagnosis, and to determine stroke subtype (IS, ICH, SAH, unknown). Because Isfahan city is the center of Isfahan province, not only patients with stroke who reside in this city but also patients who live in other cities of the province, are admitted and managed mostly in these hospitals.

Follow-Up of patients

All hospitalized patients with stroke who were discharged alive were followed by house calls/ home visits or telephone. The patients or their close family members were asked about his/her health status. If a patient had died during the first 28 days after the event, a death scenario was questioned, and stroke was considered guilty only if other etiologies, such as a motor vehicle accident, could be ruled out. We used MRS to measure functional dependency in Activities of Daily Living (ADL) at 28th-day (range 0-6; 6 denotes death and was excluded for this analysis). In the follow-up interview, functional status was questioned by using the translated Modified Rankin Scale (MRS).¹⁷

Statistical methods

The term 'stroke hospital admission rate' refers to both first and recurrent events. χ^2 for "proportion" and t-test for "mean" were used to compare proportions and means, and multiple regression model was utilized to control effects of confounding and extraneous variables. All the analysis was done with SPSS software version 20.¹⁸

Results

A total number of 10,191 patients with primary diagnoses of stroke were recorded from 2006 to 2011. However, only 9,487 (93.1%) patients met our stroke diagnostic criteria and the rest were either labeled with another diagnosis (4.6%) or remained unknown (2.3%). 9,446 (99.57%) of stroke patients were hospitalized and managed in the main 6 hospitals. Stroke verified cases constitute the sample of further analysis. Unfortunately, none of the patients were treated in a specific stroke unit or received thrombolysis (t-PA) as treatment.

Demographic data of patients with stroke is summarized in Table 1. More than 50% of hospitalized patients with stroke were males, mean age was 68.98 ± 13.63 years; the youngest was 13-year-old and the oldest was 114. While patients with SAH were the youngest group with their mean age about 14 years less than total average, those with ischemic stroke were the oldest ones. More than 85% of patients with stroke were coming from urban areas, especially Isfahan city. Although, some rural areas had access to general hospitals, we didn't make any effort to find out what percent of patients who live in rural areas actually seek treatment for stroke. Stroke subtypes were also determined and 79.6% of stroke events were of the ischemic type.

The in-hospital case-fatality rate for all types of stroke was 16.3%. Table 2 shows the potential effect of confounding factors on in-hospital case-fatality. Stroke subtype significantly affected this rate ($p < 0.001$), with the greatest one (33.9%) among patients with ICH. Patients with stroke who died, were about 3 years older ($p < 0.001$), and although statistically significant (< 0.05), death happened only a little bit more in females ($P = 0.042$). Likewise, the rate was greater among subjects with a positive stroke history ($P = 0.002$). When all the above variables were analyzed in a logistic regression model, sex was not further a significant associated/risk factor of in-hospital case-fatality rate while stroke subtype (ICH) remained the strongest contributor/risk element/factor. The ability to predict in-hospital case-fatality, especially in ischemic stroke, can help us to select high-risk patients and direct appropriate treatment. Although, chart reviews require much work and are limited in sample sizes, they provide important clinical information. Administrative data allow for large-scale analyzes but are devoid of necessary information. As a result, none of them are satisfactory enough for outcome research or case-fatality prediction. However, in one recent Japanese study, prediction of in-hospital case-fatality with accuracy similar or surpassing that

of chart review-based models, was demonstrated by the inclusion of Japanese Coma Scale (JCS), Barthel Index,¹⁷ and MRS scores in the administrative data.¹⁹

The follow-up was successful in 83% of cases over different years. It is shown that the 28th-day case-fatality rate of hospitalized patients with stroke in Isfahan was at 25.6% (Table 2). Effects of confounding factors were the same as in-hospital case-fatality; ICH had the greatest case-fatality and it was more prominent in females, elder people, and subjects with previous history stroke. Furthermore, when all of these variables were studied in a logistic regression model, stroke subtype was the greatest association/risk factor, although sex still remained significant.

Independent factors associated with early functional outcome were also investigated. This analysis demonstrated five contributing factors; ICH stroke subtype, pre-stroke disability or dependency, positive history of previous stroke, older age, and female sex, were strongly

associated with a poor functional outcome (MRS \geq 3) at 28th-day after stroke. Of all the patients who were alive at 28th-day after stroke, only 26.9% had MRS $<$ 3 (Table 3). The outcome was affected by stroke subtype and the previous history of stroke; about 50% of SAH subjects were functionally independent (MRS $<$ 3), while 85% of subjects with a previous history of stroke were functionally dependent. Male subjects had apparently better functionality than female patients, even though they were not younger. In fact, women were not significantly older than men (P=0.09). All the above variables were explicated in a logistic regression model to find out which one explained more of the variance in functional independence; the previous history of stroke was the most powerful followed by stroke subtype (ICH).

Among subjects who were functionally independent before the stroke, 34.2% had MRS $<$ 3 on post-stroke 28th-day. Patients with SAH had the best outcome; 60.0% of alive patients had MRS $<$ 3 on 28th-day after stroke followed by patients with ischemic (34.5%) and ICH (27.8%) stroke subtype (p<0.001).

Table 1 Stroke subtypes and patients' demographic data in Isfahan hospitalized stroke patients, from 2006 to 2011

	Stroke subtypes			Total
	Ischemic	ICH	SAH	
Number n(%)	7,548 (79.6)	1,628 (17.2)	183 (1.9)	9,487 (100)
Male sex n(%)	3,893 (51.7)	838 (51.6)	76 (41.8)	4,881 (51.4)
Female sex n(%)	3,639 (48.2)	787 (48.4)	106 (58.2)	4,586 (48.3)
Age\pmSD, years				
Mean	69.77 \pm 13.12	66.75 \pm 14.52	54.96 \pm 16.65	68.98 \pm 13.63
Min	14	13	18	13
Max	114	110	113	114
Settlement				
Urban				8,089 (86)
Isfahan city	4820 (64.3)	893 (55.4)	99 (55.3)	5,916 (62.9)
Other cities	1658 (22.1)	449 (27.8)	51 (28.5)	2,173 (23.1)
Rural				1,322 (14)
Isfahan city area	341 (4.6)	77 (4.8)	6 (3.4)	426 (4.5)
Other cities areas	673 (9.0)	194 (12.0)	23 (12.8)	896 (9.5)

ICH=Intracerebral hemorrhage; SAH=subarachnoid hemorrhage; SD=standard deviation; Figures in parentheses indicate percentages

Table 2 Potential effect of confounding factors on case-fatality rate among Isfahan stroke hospitalized patients, from 2006 to 2011

	In-hospital	P-value	28th day	P-value
All Stroke subtypes (n=9487)	16.30%	<0.001	25.60%	<0.001
Ischemic	12.50%		21.20%	
ICH	33.90%		44.80%	
SAH	23.50%		30.90%	
History of previous stroke		0.002		0.001
Negative	15.50%		24.30%	
Positive	18.20%		28.20%	
Sex		0.042		0.006
M	15.60%		24.20%	
F	17.20%		27.00%	
Age (Mean\pmSD)		<0.001		<0.001
Alive	68.39 \pm 13.68		68.08 \pm 13.43	
Dead	71.96 \pm 13.06		73.37 \pm 12.71	

ICH=Intracerebral hemorrhage; SAH=subarachnoid hemorrhage; SD=standard deviation. Figures in parentheses indicate percentages

Table 3 Potential effect of confounding factors on functional outcome at 28th-day among Isfahan stroke hospitalized patients, from 2006 to 2011

	MRS<3 (Total)	P-value	MRS <3 (if Pre-stroke MRS <3)	P-value
All Stroke subtypes	26.90%	<0.001	34.20%	<0.001
Ischemic	27.40%		34.50%	
ICH	20.60%		27.80%	
SAH	49.50%		60.00%	
History of previous stroke		<0.001		
Negative	30.80%			
Positive	15.60%			
Sex		0.001		
M	28.70%			
F	24.90%			
Age (Mean±SD)		<0.001		
MRS < 3	62.62±14.59			
MRS ≥ 3	70.09±12.38			

SD=standard deviation; MRS=Modified Rankin Scale; Figures in parentheses indicate percentages

Table 4 Our study sample sex and age distribution in comparison with Brazil and USA^{19,20}

	Brazil	USA	Iran
Mean Age			
Total	67.7±14.4	69.6 ± 0.1	68.98 ± 13.63
Ischemic	69.14 ± 13.6		69.77 ± 13.12
ICH	62.70 ± 14.9		66.75 ± 14.52
Sex (f)			
Total	51.80%	53.3	48.3
Ischemic	50.10%		48.2
ICH	47.50%		48.4
Previous history of Stroke			
Total	42.90%		18.20%
Ischemic	46.20%	30.7	
ICH	33.30%	20.3	

Discussion

Amongst the factors which were independently linked to case-fatality, the ICH stroke subtype and older age were the strongest, followed by a history of the previous stroke. The in-hospital case-fatality rate in this study was at 12.5% for ischemic stroke and 33.9% for ICH subtype which was considerably greater than a similar study conducted with 56,969 patients enrolled in the USA, yielding an overall case-fatality rate at 6.8%; 5.7% for IS and 22.7% for hemorrhagic stroke.²⁰ On the contrary, our findings had a resemblance to a recent study which was done with 2,407 patients evaluated in Brazil, demonstrating overall case-fatality of 20.9% with stroke subtype case-fatality rate at 17% for ischemic stroke and 34.1% for ICH.²¹ The stroke subtype 28th-day case-fatality in our study reached at 21.2% for ischemic stroke and 44.8% for ICH. These percentages can be compared to the 28th-day case-fatality rates in low and middle-income countries classified by the World Bank.²² at 16.7% for ischemic stroke and 38.7% for ICH.²³

The greater in-hospital and the 28th-day case-fatality rate in our study relative to developed countries could be attributed to the preference for admission of more patients with severe stroke due to lack of sufficient facilities. In addition, it could reflect using low-quality standards of care for patients with acute stroke. These may include significant delays in hospital admission, diagnosis, and evaluation with Neuro-imaging, absence of thrombolytic use for patients with ischemic stroke; mostly due to arriving at the hospitals after the approved time limit (3-4.5 hr from the beginning of stroke) or even unavailability of t-PA in the hospitals, and lack of both stationary and mobile stroke units for treatment of patients with stroke.

Table 4 shows our study sample sex and age distribution in comparison to hospitalized patients with stroke in Brazil and USA, which are nearly the same. This excludes confounding effect of age and sex in the differences seen between the countries. Since the factor of the previous history of stroke was significantly smaller in our study, it couldn't also explain the greater case-fatality observed in Iran.

Furthermore, another factor explaining this finding might be the different medical care for stroke in Iran compared to most developed countries. Indeed, none of our studied patients were managed in a stroke unit or received t-PA which might contribute to increased case-fatality or poor functional outcome, and hence necessitate the use of early interventions to modify this national problem. Stroke Unit is a highly evidence-based approach, shown to improve outcome after stroke. A systematic meta-analysis investigating stroke units showed 18% reduction in the risk of case-fatality and dependency.⁴ One of the major limitations to the implementation of stroke units in Iran is the restricted availability of stroke specialists as well as the paucity of technical and financial capacity. Other possible obstacles are the shortage in health resources, disregarding the stroke as a priority health problem, and inadequate training of health personnel.

The strength of our study includes the collection of data from all patients with stroke admitted to six Isfahan hospitals, which provide the vast majority of stroke care in this area, a successful follow-up in more than 83% of patients, and acquisition of functional status during the follow-up. However, it has also some limitations as being non-population-based, not covering patients with stroke who were not hospitalized; use of hospital records to get history and risk factor profiles, not doing Magnetic Resonance Imaging (MRI) for all

possible ischemic stroke with normal CT scans, and diagnosing stroke by clinical history and exams. The scrutiny of standards for stroke management, especially in the hospitals with specific neurology wards was restrained by lack of local resources and sufficient evidence. We didn't compare the quality of care, case-fatality and morbidity rates between hospitals with neurology wards and those with only internal medicine wards. Since none of the hospitals with specific neurology wards had stroke units or followed a standard protocol for stroke treatment, we concluded that the results of such comparison would not change the decision regarding the urgent need for employment of stroke units and other facilities to increase the chance of receiving treatment with t-PA in eligible patients with ischemic stroke and improving outcome.

Conclusion

In summary, these findings are important as they demonstrate that outcome following stroke is poor in Isfahan as a reliable representative of stroke outcome in Iran. The global impact of stroke in Iran, similar to other low and middle-income countries, is taking a disproportionate toll on its people. This study of 9,487 patients with stroke from Isfahan hospitals, highlights the greater early case-fatality and disability due in part to the lack of specialized stroke units and hence receiving approved management. Investigation of standards of care was limited by lack of local resources and evidence. Expectedly, none of the patients with ischemic stroke received t-PA as an FDA-approved treatment. This finding can reflect the lack of stroke units, scarcity of this drug in our hospitals, arriving at hospitals after the golden time, and absence of experienced stroke specialists. Although, our research doesn't definitely demonstrate that general care within our hospitals is poor, the data do provide support for an implementation research to improve outcome in hospitalized patients. We commend the other investigators for taking up the task of performing an epidemiological survey of stroke outcome in our community and recognizing the need for improving the quality of care for patients with stroke. In the future work, we hope to facilitate implementation and sustainability of widely accepted, and locally feasible, standards of care through building stroke units or using recently introduced mobile stroke units (MSU) that have the potential to reduce the burden of stroke in Iran and other neighboring nations facing this problem. Although, the building of stroke units and setting standard of care for patients with stroke is important, it is equally significant to educate and increase awareness of the general population about different aspects of stroke as the window of opportunity to successfully treat patients with stroke is short. So, it is obvious that simple, inexpensive interventions to improve outcome or reduce recurrent stroke and case-fatality rate should not be ignored.

Acknowledgements

This study was supported by grant number 91116 from Isfahan Cardiovascular Research Institute. We would like to thank our staff who helped us in data gathering and verification: Mahtab Sepahifar, Farzaneh Nilforooshzadeh, Leila V. Dalili, Zahra Ghorbani, and Zahra Kiani. Also, we greatly appreciate all Isfahan hospitals' managers (mostly Alzahra's, Shariati's, Gharazi's, Kashani's, Amin's, Sadooghi's, and Zahra Marzieh's) for their cooperation.

Conflicts of interest

None.

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